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Ghrelin, leptin and adiponectin as possible predictors of the hedonic value of odors

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ABSTRACT

Several lines of evidence point to a close relationship between the hormones of energy homeostasis and the olfactory system. Examples are the localization of leptin and adiponectin receptors in the olfactory system or increased activation of brain regions related to the palatability and the hedonic value of food in response to food pictures after application of ghrelin.

In this preliminary study, we tested in 31 subjects (17 male and 14 female) if and to what extent the peripheral blood concentrations of "satiety" hormones, such as leptin, adiponectin, and ghrelin (acyl and total), are correlated with the self-ratings of odor pleasantness and with the objective olfactory and gustatory ability.

The hedonic values of some odors were found to be differently rated between donors depending on gender and body weight. The concentrations of leptin, adiponectin and total ghrelin were significantly associated with the hedonic value of pepper black oil, but failed to show significant correlations for 5 other odors tested. Except for a significant association between leptin and odor identification, hormone concentrations were not linked to the abilities of smell and taste.

Peripheral adipokines and gut hormones may alter the perception and pleasantness of specific odors, presumably either directly through their receptors in the olfactory system or indirectly through central interfaces between the regulation systems of olfaction, appetite control, memory and motivation.

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1. Introduction

Adipokines, e.g. leptin and adiponectin, are adipose tissue-secreted factors, involved in the energy homeostasis, food intake, immunity and neuroendocrine systems [1–3]. Gut hormones, such as ghrelin, are released by the gastrointestinal tract and modulate the activity of central "appetite and satiety centers" leading to a change in ingestive behavior [4,5]: Ghrelin administration increases appetite and food intake in animals [6] as well as in humans [7]. Plasma ghrelin levels show a preprandial rise and postprandial fall, initiating meals without food-related cues [8]. In addition to hypothalamic ghrelin [9], peripheral ghrelin is able to reach the brain through the blood-brain barrier [10] and to activate the hypothalamic NPY/AgRP (neuropeptide Y/agouti-related protein) orexigenic pathway via interactions with the growth hormone secretagogue receptor (GHS-R) [6,11,12]. Only acyl-ghrelin, a form acylated at serine 3, binds to GHS-R and thus has been initially designated as ("active") ghrelin. However, 80–90% of circulating ghrelin is not acylated (des-acyl-ghrelin), but seems to induce food intake by mechanisms independent of GHS-R [13–15].

Olfactory and gustatory information is a major factor determining the palatability and the hedonic value of food and thus influencing food intake [16,17]. Olfactory bulbectomy may alter the feeding pattern of rats [18,19]. In humans, intranasal lidocaine seems to reduce hunger ratings [20]. Various facts point to a close relationship between the hormones of energy homeostasis and the olfactory system: For example, receptors of adiponectin are found in the olfactory mucosa of mice [16]. Also leptin receptors are expressed in the olfactory mucosa and upregulated by fasting [21]. Furthermore, leptin receptors are found in the olfactory bulb [22] and the piriform cortex [23]. In mice, leptin could modulate olfactory-mediated pre-ingestive behavior through leptin receptors [24]. In humans, a gender-specific relation between leptin and the ability to identify an odor was observed [25]. Activation of parts of the human orbitofrontal cortex was reported to correlate with subjective ratings of pleasantness regarding the taste and smell of food [26]. Thus, the orbitofrontal cortex, together with the amygdale and striatum, has been suggested as the brain region which links olfactory and other sensory stimuli with reward, motivation and the incentive value of food cues [12,26,27]. Supporting this idea, ghrelin, administered intravenously to healthy humans, increases the neural response to food pictures in

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these brain regions [12]. This demonstrates that metabolic signals such as ghrelin may enhance the hedonic responses to olfactory cues.

Thus, the regulation of "satiety" hormones, such as leptin, adiponectin, and ghrelin, and the olfactory system seem to interact closely. Here we tested if and to what extent the peripheral blood concentrations of these "satiety" hormones are correlated with the self-ratings of odor pleasantness and with the objective olfactory and gustatory ability. Gender and body mass index (BMI) were considered as possible influence factors. We found that peripheral adipokines and gut hormones may alter or predict the perception and pleasantness of specific odors. This pilot study encourages further studies how odor perception is linked to the peripheral metabolism, possibly leading to novel insights useful for the general application of odors and flavors as well as for the treatment of obesity.

2. Materials and methods

2.1. Study subjects

Thirty-one young healthy subjects (European; 17 male, 14 female; median age, 29 years; range, 20–45 years) were recruited for the study. The most important selection criterion was BMI, so that we would be able to analyze study groups of similar size with normal weight, overweight and obesity. The BMI of the subjects ranged between 20.2 and 54.5 kg/m^2 (median 28.1 kg/m^2). Furthermore, gender should be well distributed in our cohort and considered in the statistical analysis. In particular, 6 men and 4 women were selected with BMIs between 20 and 25 kg/m^2, 5 men and 4 women between 25 and 30 kg/m^2, and 6 men and 6 women with BMI larger than 30 kg/m^2 (obesity) were included. The experiments were approved by the local ethics committee. Written informed consent was obtained from all subjects before samples were collected.

The subjects were recruited by notice and blinded with respect to the aim of the study using a cover story suggesting that the primary aim of the study was a questionnaire evaluation. Out of more than 200 subjects, 48 were invited for preliminary examination. On this first morning, young healthy subjects were selected by using a variety of interdisciplinary medical exclusion criteria and examinations. In detail, we checked the following exclusion criteria: history of neurologic or psychiatric illness, gastrointestinal and eating disorder and surgery (also detection of *Helicobacter pylori*, but not history of appendectomy), diabetes and other endocrinological disorders (e.g. polycystic ovarian syndrome), history of smelling disorder, impaired nasal breathing or history of sinus surgery, BMI$<$20 kg/m^2, regular tobacco use, pregnancy or breastfeeding, most kinds of medication (e.g. contraceptives), and acute cold or infection. Subjects with an age under 18 or above 45 years were excluded.

All subjects underwent an otorhinolaryngological and general medical examination. Colonization with *H. pylori* was excluded by a C^{13} urea breath test. Peripheral blood measurements included a differential haemogram, HbA1c, fasting blood sugar, creatinine, hepatic enzymes, testosterone, and TSH. Urine was checked by test strips, especially regarding glucosuria. The subjects had to give self-ratings on 100 mm visual analog scales about various abilities including their sense of smell and nasal breathing. A German version of the Eating Disorder Inventory (EDI-2) [28], a questionnaire about eating behavior (FEV) [29] and a patient health questionnaire for screening of anxiety and depression (PHQ-D) [30] were used to exclude potential subjects with abnormal eating behavior and screen for possible psychological disorders. Altogether, all criteria mentioned resulted in exclusion of 17 subjects for further examination.

BMI was calculated as measured body weight (kg) divided by measured height (m) squared. Ratio of body fat was measured by Body Impedance Analyzer Modell BIA 101 and BodyComp. V8.3 software (Medical Healthcare GmbH, Karlsruhe, Germany).

2.2. Course of main examination

Men were examined on the next possible day, while women had to come within the first week of menstrual cycle. All sessions started between 8 and 9:30 a.m. Subjects were requested to be in a fasting condition for a minimum of 10 h. After preparing an intravenous approach and a period of 15 min, a first blood sample was taken as internal control. Then, subjects had to spend 30 min with a set of psychological questionnaires (cover story), before the main blood sample was taken for measurement of the "satiety" hormones. Finally, an olfactory and gustatory testing was performed.

2.3. Olfactory and gustatory testing

We used six essential oils applied in 200 mL boxes, containing about 0.35 ± 0.03 g of the essential oil and offered to the subjects in unchanging order. In particular, these were "grapefruit" (grapefruit oil Florida), "fennel" (fennel oil sweet fly), "pepper" (pepper black oil), "lavender" (lavender oil Mont Blanc), "patchouli" (patchouli oil genuine), and "rose" (rose oil Bulgarian) which we received from Symrise GmbH & Co. KG (Holzminden, Germany) including gas chromatographic analyses of all oils. Pleasantness and intensity of odors were rated by 100 mm VAS and their recognition and description were asked.

Olfactory function was assessed by using Sniffin' Sticks (Burghart Instruments, Wedel, Germany). In this test, the olfactory detection threshold is determined by using 16 dilution steps of n-butanol and means of a single-staircase, three alternative forced choice procedure. Odor discrimination was tested using 16 triplets of odorants and also a three alternative forced choice procedure. The ability of odor identification was evaluated by 16 commonly known odorants which have to be judged in relation to one of four descriptors each. The sum of the results of these three Sniffin' Sticks subsets is called "TDI score" and represents a validated score for the description of olfactory function [31].

Examination of taste was performed by using taste solutions of sodium chloride (salty), saccharin (sweet), citric acid (sour), quinine (bitter), sodium glutamate (umami), and water (as control) with ascending concentrations to determine perception thresholds, respectively.

2.4. Peripheral blood analyses

Blood was processed at a temperature below 4 °C at all time points including centrifugation and then stored at −80 °C until analysis. Concentrations of leptin, adiponectin, and total ghrelin were determined with Bio-Plex Diabetes Assays (Bio-Rad Laboratories, Hercules, CA) according to the manufacturer's instructions. Therefore, the sample tubes were prepared with EDTA (Sarstedt, Numbrecht, Germany), the protease inhibitor Pefabloc SC (Carl Roth, Karlsruhe, Germany) and a DPP-IV inhibitor (Millipore, Billerica, MA). Acyl ghrelin was determined by enzyme linked immunosorbent assay (DRG Diagnostics, Marburg, Germany) according to the manufacturer's instructions. Therefore, EDTA plasma including Pefabloc and DPP-IV inhibitor was acidified additionally with HCl.

2.5. Statistical analysis

Standard descriptive statistics were used to summarize the data (e.g., means and standard deviations (SD)). To assess between group differences related to obesity or gender, we used non-parametric testing (Wilcoxon–Mann–Whitney test). Correlation coefficients reported are (Spearman) rank correlations. For further analysis of association between hedonic rating of odors, olfactory and gustatory testing and blood values, we used (generalized) linear regression analysis.

All reported *P*-values are nominal, two-sided, and not adjusted for the testing of multiple hypotheses, i.e. we applied a significance level α of 0.05 for each statistical test. SPSS Version 16 (SPSS Inc., Chicago, IL) was used for statistical analyses.

3. Results

3.1. Overview on odor pleasantness

At first, we analyzed the pleasantness of six (grapefruit oil Florida, fennel oil sweet fly, pepper black oil, lavender oil Mont Blanc, patchouli oil genuine, and rose oil Bulgarian) essential oils using 100 mm VAS. Below, we use the terms "grapefruit", "fennel", "pepper", "lavender", "patchouli", and "rose" for simplification. Ratings of odor pleasantness were observed across the whole range of the VAS from 0 mm (lowest pleasantness) to 100 mm (highest pleasantness). The distribution was approximately normal (median 47 mm; mean 47.1 ± 30 mm (SD)). Grapefruit and fennel were rated most pleasant, followed by lavender and rose (Fig. 1). Pepper oil and patchouli oil got the lowest ratings. Despite of the time waited between each rating and the large interindividual variance of ratings observed, each rating of the next odor was scored significantly differently to the one odor before, with a *P* in a range from <0.001 to 0.006 (Fig. 1).

Subgroup analyses revealed no evidence for an association between gender and the general rating of odor pleasantness ($P = 0.71$) whereas the explorative comparison of obese (BMI>30 mg/kg^2) in comparison to the non-obese subjects (BMI<30 mg/kg^2) revealed slightly larger values in the later group (obese: median 42 mm; mean 42.0 ± 32.9 mm; non-obese: median 50 mm; mean 50.4 ± 27.7 mm; $P = 0.057$).

3.2. Pleasantness of specific odors is related to gender and body weight

Next, ratings of odor pleasantness were analyzed depending on gender and body weight for every single odor tested (Fig. 2). For patchouli oil, male subjects (median 26; mean 32.3 ± 22.3) showed a significantly higher odor pleasantness than females (median 9.5; mean 14.4 ± 13.5) ($P = 0.005$ for gender, $P = 0.49$ for BMI). Subjects with a BMI<30 kg/m^2 rated pepper oil significantly more pleasant (median 32; mean 37.9 ± 26.6) than obese subjects (median 6; mean 15.2 ± 17.2) ($P = 0.09$ for gender, $P < 0.001$ for BMI).

As the rating of one odor may be influenced by the one before, we related the ratings of two consecutively tested odors by counting the difference of their ratings (e.g. VAS (fennel) minus VAS (pepper)) for further analysis. By testing BMI higher versus lower 30 kg/m^2, there was a worse significance for VAS (fennel) minus VAS (pepper) ($P = 0.117$) compared to VAS (pepper) alone ($P = 0.009$). By using the factors gender and BMI, a significance value $P = 0.001$ for BMI was calculated with the dependent variable VAS (fennel) minus VAS (pepper) (data not shown). Using the difference VAS (lavender) minus VAS(patchouli) leads to a significance of $P = 0.018$ for gender compared to $P = 0.005$ for VAS(patchouli) alone (see above). Therefore, taking into account the preceding odor does not improve the significances observed. Altogether, gender and body weight seem to be major influence factors for the pleasantness of specific odors.

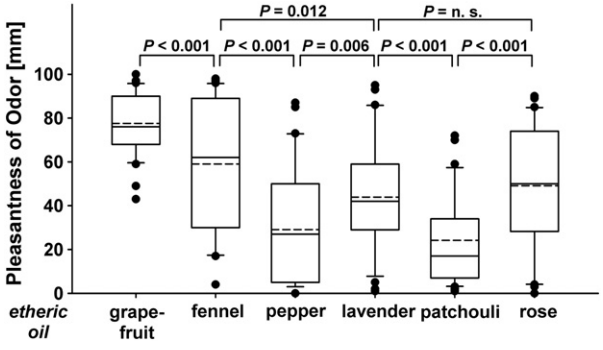

Fig. 1. Different hedonic values of odors. A panel of essential oils (grapefruit oil Florida, fennel oil sweet fly, pepper black oil, lavender oil Mont Blanc, patchouli oil genuine, and rose oil Bulgarian) was rated regarding odor pleasantness on 100 mm visual analog scales (lowest hedonic value 0 mm, highest 100 mm) by healthy subjects. Given are the median, percentiles (10th, 25th, 75th, and 90th), and mean (dashed line) as vertical boxes with error bars; outliers are shown as dots. *P* values (Mann–Whitney) are indicated. The odors differed in their hedonic value, marked-off one to the one before.

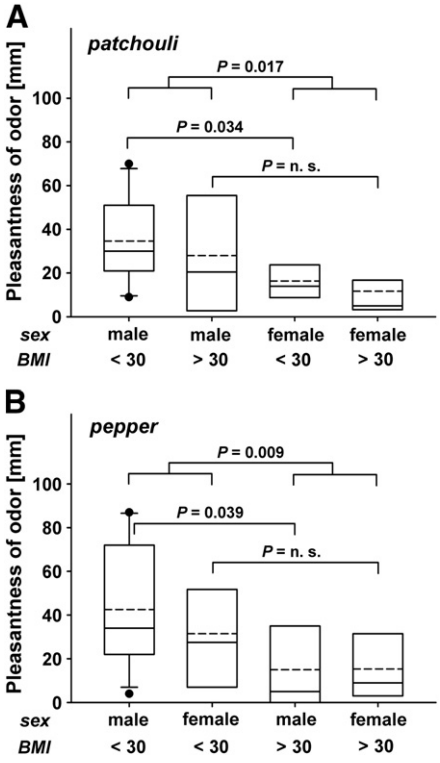

Fig. 2. Pleasantness of specific odors is associated to gender and body weight. Pepper black oil (A) and patchouli oil genuine (B) were rated regarding odor pleasantness on 100 mm visual analog scales (lowest hedonic value 0 mm, highest 100 mm) and analyzed in consideration of gender and body mass index (BMI, [mg/m^2]). Given are the median, percentiles (10th, 25th, 75th, and 90th), and mean (dashed line) as vertical boxes with error bars; outliers are shown as dots. *P* values (Mann–Whitney) are indicated. A low hedonic value of "pepper" is associated to obese subjects, while a low hedonic value of "patchouli" is associated with female gender.

3.3. Pleasantness of odors in relation to hormones

Next, we compared the pleasantness of odors in relation to the adipokines leptin and adiponectin, and the gut hormone ghrelin (acyl and total). Therefore, first graphical analysis by scatter plots (Fig. 3), then correlation testing and (generalized) regression analysis were performed for all subjects (Table 1). This analysis showed that the pleasantness ratings of pepper oils seem to be associated with the concentration of leptin, adiponectin, and total ghrelin, but not acyl ghrelin. Thus, additional to gender and BMI, concentrations of these hormones may enable predicting the hedonic value of some odors.

3.4. Olfactory and gustatory testing in relation to gender and weight

In the pooled study group, the olfactory testing with Sniffin' Sticks (see Materials and methods) yielded results according to the expectations (Olfactory detection threshold: median, 9, mean 9.13 ± 2.45; olfactory discrimination: median 13; mean 12.74 ± 1.63; olfactory

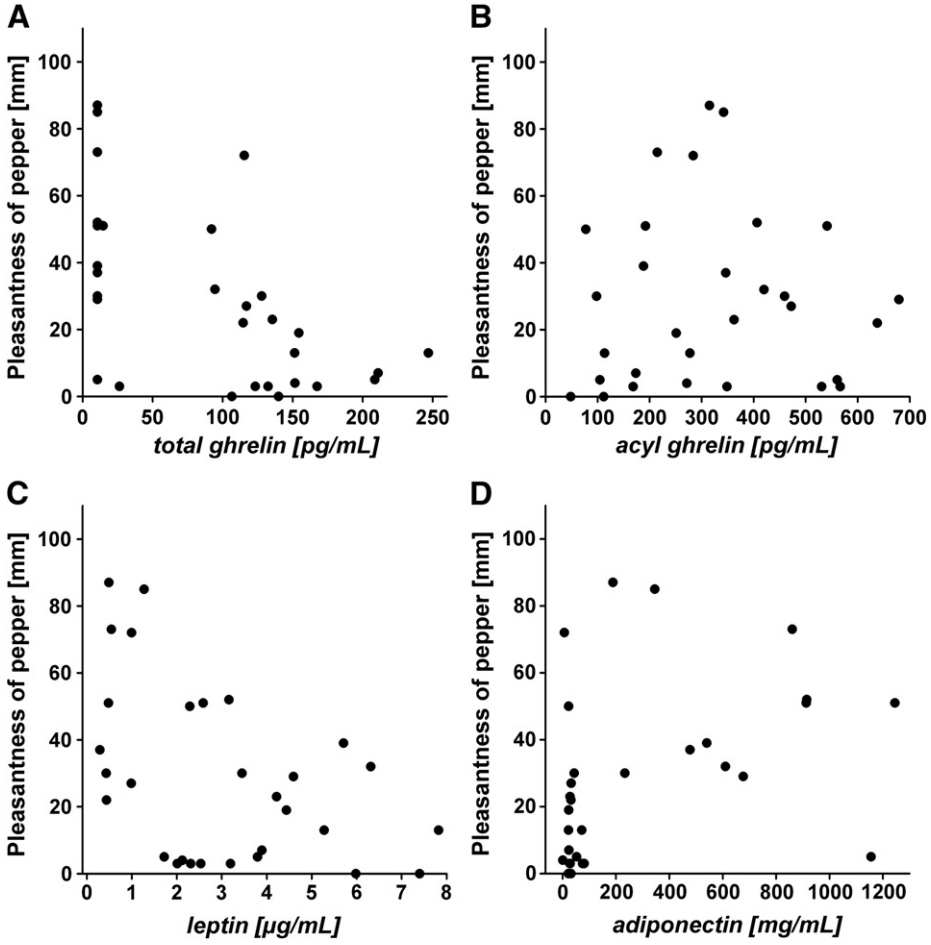

Fig. 3. The hedonic value of pepper is associated with serum concentrations of leptin, adiponectin and total ghrelin. Shown are scatter plots with the concentration of total ghrelin (A), acyl ghrelin (B), leptin (C), and adiponectin (D) as x-axis and the odor pleasantness of pepper black oil, rated on 100 mm visual analog scales. Total ghrelin and leptin were negatively, adiponectin was positively, while total ghrelin was not correlated to the hedonic value of pepper black oil. For further statistical analysis see Table 1.

identification: median 14, mean 13.55 ± 1.57; "TDI-score": median 35.25, mean 35.42 ± 3.80). No significant difference was observed in relation to gender or BMI (data not shown). The gustatory testing with taste solutions results in following thresholds of perception (median, mean ± SD [mmol]): sodium chloride 100, 80.3 ± 54.3, citric acid 10, 9.23 ± 7.92, saccharin 0.030, 0.070 ± 0.074, quinine 0.03, 0.063 ± 0.073, sodium glutamate 1, 5.07 ± 8.88. Gender represented no significant influence factor on these thresholds. The group of obese subjects had a higher threshold of perception for quinine and sodium glutamate compared to the subjects with BMI < 30 kg/m^2 (quinine [mmol]: median 0.065, mean 0.082 ± 0.077 versus median 0.03, mean 0.050 ± 0.070, $P = 0.036$; sodium glutamate [mmol]: median 3, mean 7.83 ± 3.22 versus median 1, mean 3.22 + -7.02, $P = 0.033$). Using the factors BMI and gender showed no significant P value for both factors and both taste

Table 1
Statistical analysis on the association between hormone measurements and olfaction.

	Dependent	Correlation testing		Regression analysis		Generalized linear model (3 influence factors)			
	Variable	Coefficient	P	Beta	P	Omnibus test	P (hormone)	P (gender)	P (obesity)
Hormone									
Total ghrelin	Pepper bl. Oil[a]	−0.626	<0.001	−0.581	0.001	0.001	0.001	0.215	0.067
Adiponectin	Pepper bl. Oil	0.451	0.012	0.379	0.039	0.008	0.025	0.071	0.087
Leptin	Pepper bl. Oil	−0.411	0.024	−0.462	0.010	0.024	0.119	0.823	0.129
Leptin	Odor identification [b]	0.384	0.036	0.377	0.040	0.188	0.087	0.680	0.913
Examples of non-significant results:									
Acyl ghrelin	Pepper bl. oil	0.105	0.583	0.028	0.883	0.046	0.334	0.691	0.005
Acyl ghrelin	Odor identification	−0.051	0.789	0.000	0.999	0.571	0.944	0.335	0.421
Total ghrelin	Odor identification	0.283	0.130	0.318	0.087	0.180	0.081	0.208	0.754
Adiponectin	Odor identification	−0.115	0.546	−0.078	0.683	0.485	0.502	0.203	0.584
Leptin	TDI-Score[c]	−0.010	0.957	0.026	0.890	0.849	0.521	0.697	0.396

[a] Pleasantness of pepper black oil, rated on 100 mm visual analog scales.
[b] According to [30] by using Sniffin' Sticks.
[c] According to [30] by using Sniffin' Sticks and summing olfactory detection threshold, discrimination and identification scores.

solutions. Altogether, our study group showed no crucial differences in these olfactory and gustatory tests depending on gender and weight.

3.5. Olfactory and gustatory testing in relation to hormones

Finally, we analyzed the association of the hormones measured to the olfactory and gustatory testing. No significant association was observed for adiponectin, acyl and total ghrelin for every parameter of smell and taste measurements (data not shown). Only the leptin concentration may be positively associated with the ability of odor identification for all subgroups according to the statistical results (Table 1). If ratio of body fat was used as factor in the generalized regression analysis, this results in $P=0.002$ for leptin, $P=0.190$ for gender, and $P=0.023$ for the ratio of body fat (data not shown).

Thus, further studies are required to unequivocally elucidate the importance of adipokines and gut hormones in the perception and hedonic processing of odors. A careful demarcation of further influence factors as gender and body weight should be included in future studies with larger and more homogeneous cohorts.

4. Discussion

This pilot study aimed to test the hypothesis that the peripheral blood concentrations of "satiety" hormones, such as leptin, adiponectin, and ghrelin, correlate with the self-ratings of odor pleasantness and with the objective olfactory and gustatory ability. We have chosen these hormones as they play an important role in both the peripheral and central regulation of energy homeostasis and feeding behavior [1,3,4,12]. Additionally, their receptors are found in different levels of the olfactory system [16,21,23]. Furthermore, recent research points at a reciprocal association between ghrelin, the central processing of sensory perceptions and the palatability of such perceptions: Ghrelin administered intravenously increases the neural response to food pictures in brain regions related to the hedonic value of food odor and taste [12]. On the other hand, sensory food-related stimuli may regulate ghrelin secretion in rats [32], and humans [33]. Thus, understanding and deciphering further details on this regulatory system may help to predict human eating behavior and may enable future possibilities of intervention within this system as novel therapeutic strategies for the treatment of obesity [34].

Therefore, a well-defined, young, healthy and blinded study population was used in this study. We took into account possible influences by gender and body weight in consideration of their different olfactory perception [35–37] and their different effects on hormone levels and hormone responses [38,39]. We found that higher pleasantness of pepper black oil was associated with lower body weight. Patchouli oil genuine exerted a more positive perception in males compared with females.

A possible explanation for this variation between the odors of pepper and patchouli is their diverging relation to food. This is supported by the observation that the olfactory detection threshold and pleasantness of the food-related odor isoamyl acetate decreases after a meal in contrast to unchanged levels for the non-food odor n-butanol [40]. Interestingly, pepper as well as patchouli was scored with the lowest rating of pleasantness among all odors tested. The fact that pleasant and unpleasant odors are linked to different brain regions [41] may cause these subgroup differences for rather unpleasant odors. Another possible explanation comes from the observation that, in humans, inhalation of pepper oil has been linked to an increase of sympathic activity in contrast to a decrease observed for patchouli oil [42]. Furthermore, the different sympathic nervous activity depending on gender and BMI [43], the changes of the sympathic–parasympathic balance related to satiety [44], and the influence of autonomic responses on the sensory pathways via the lateral hypothalamus [26] may further explain and influence the connection between sympathic activity of odors and odor pleasantness. Nevertheless, the regulation systems mentioned are very complex, involving many intrinsic and extrinsic factors, so that further studies are needed to confirm and extent the findings of this study.

In our study, the blood concentrations of total ghrelin, adiponectin and leptin, but not acyl-ghrelin, correlated with the pleasantness of the "activating" odor of pepper black oil. The different results for acyl and total ghrelin are consistent with the different effects of acyl and desacyl ghrelin in food intake and receptor interaction observed recently [14,15]. The other odors tested failed to show significant correlations. Furthermore, the leptin concentration may be positively associated with the ability of odor identification. Odor identification is not only a matter of sensory function, but also considered in close reliance on memory and learning [45]. Growing evidence shows that an enhancement of various cognitive functions, especially learning and memory, is regarded to an increased leptin level [46,47] and thus may lead to an improved odor identification observed in this study. Hence, peripheral adipokines and gut hormones may alter the perception and pleasantness of specific odors, either directly through their receptors in the olfactory system or indirectly through central interfaces between the regulation systems of olfaction, appetite control, memory and motivation.

This explorative study contains some methodological restrictions leading to possible improvements/alterations in future studies. With more permissive exclusion criteria, following studies may improve with bigger number of subjects and exclusion of BMI 25-30 kg/m^2 for better inter-group comparisons (normal weight versus obesity). As BMI as well as gender seem to be influence factors, selection of only a single cohort property may be recommended regarding the cohort homogeneity and thus reliability of results. A repeated session with the same individuals could be performed at different days to compare intra-individual variability. As odor pleasantness depends on odor concentration [48], a testing with various odor concentrations could be useful. Furthermore, as attention to the affective value alters how the brain processes olfactory stimuli [49], it was interesting to examine odor perception, pleasantness and effects for different grades of attention in subjects. As a normal matter of statistical interpretation, correlations and associations shown are no proof of causality. To this aim, a variation of adipokines or gut hormones, e.g. as intravenous application, could be included into future studies.

In conclusion, this study supports the idea that peripheral adipokines and gut hormones may alter or predict the perception and pleasantness of specific odors. Improved knowledge on links between odor perception and peripheral metabolism could lead to useful insights for the general application of odors and flavors as well as to novel therapeutic strategies for the treatment of obesity.

List of abbreviations

BMI	body mass index
GHS-R	growth hormone secretagogue receptor
VAS	visual analog scales

Conflict of interest statement

This study included financial support kindly provided by Symrise GmbH & Co. KG (Holzminden, Germany).

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